Amendments to the Specification

In the Specification:

Please amend the specification as shown:

Please delete paragraph [0039] and replace it with the following paragraph:

[0039] The insulin molecule may be native human insulin (see the sequence of native human insulin below in Formula I) or an analogue thereof such as an insulin molecule with amino acid substitution(s), amino acid deletion(s) or amino acid addition(s). The following are listed as examples of insulin analogue that can be used in accordance with the present invention without the intention to limit the present analogue in any way: insulin glargine called **LANTUS**® of Aventis Pharmaceuticals Inc., which has a glycine substituted in position A21 and two residues of arginine added in C-terminus of the chain B; insulin detemir called **LEVEMIR**® of Novo Nordisk A/S, which is a native human insulin where threonine in position B30 is deleted and tetradecanoyl is added on the lateral chain of lysine B29; insulin lispro called **HUMALOG**® of Eli Lilly, which is Lys B28, Pro B29 human insulin; insulin aspart called **NOVOLOG**® of Novo Nordisk A/S, which Asp B28 human insulin; and insulin glulisine called **APIDRA**® of Aventis, which is Lys B3, Glu B29 human insulin.

Please delete paragraph [0060] and replace it with the following paragraph:

[0060] Flash column chromatography was carried out using a **BIOTAGE**® "40i flash chromatography" modular system. Semi preparative HPLC purifications were done on a Waters "Breeze" system 1500 series using a Phenomex luna (RP-18, 10 u phenyl-hexyl 250×21.2 mm) column with a 9.5 mL/min mobile phase flow rate. A Gilson 690 system was used for preparative scale purification using a Phenomex luna (RP-18, 10 u phenyl-hexyl 250×50.0 mm) column With a 50 mL/min mobile phase flow rate. A Gradient of acetonitrile (CH_3CN) (0.1% TFA) in water (0.1% TFA) was used with further details indicated in each compound's synthetic procedure. LC-MS was performed using an Agilent 1100 series LC-MSD single quadrupole mass spectrometer with an ES1 electrospray source.

Please delete paragraph [0069] and replace it with the following paragraph:

[0069] MPA-$(AEES)_2$-COOH (3.04 g) was dissolved in N,N-dimethylformamide (20 mL) and the presence of NMM (1.13 mL) and treated with p-nitrophenyl chloroformate (1.13 g). The reaction mixture was stirred at ambient temperature for 2 h. N,N-dimethylformamide was removed under vacuum. The residue was purified by flash column chromatography using **BIOTAGE**® system. The column was rinsed with ethyl acetate (500 mL) followed by 10% methanol in ethyl acetate (1 L). The pure fractions were combined and the solvent removed to give MPA-$(AEES)_2$-CO_2 PNP as a solid (1.39 g, 37%). MS m/z 663.

Please delete paragraph [0073] and replace it with the following paragraph:

[0073] Liver membranes of Wistar rats were incubated with [125I] insulin and increasing concentrations of insulin, **DAC™**:insulin as described in FIG. 1 and their corresponding conjugate for 16 hours at 4° C. The membranes were filtered and washed 3 times and the filters were counted to determine [125I] insulin specifically bound. IC50 were calculated using GraphPad **PRISM™** software.

Please delete paragraph [0077] and replace it with the following paragraph:

[0077] 3T3-L1 adipocytes were starved overnight in DMEM containing 5 mM glucose and 0.5% FBS. Cells were rinsed in Kreb's-Ringer-Hepes buffer containing 1% BSA and incubated with increasing concentrations of insulin, **DAC™**:insulin derivatives and their corresponding conjugate for 20 minutes at 37° C. and with [^{14}C]-2-deoxy-D-glucose (1μCi/well) for an additional 20 minutes. Cells were solubilized and radioactivity was measured. Glucose uptake (%) was calculated versus insulin control and EC50 were calculated using GraphPad **PRISM™** software.

Please delete paragraph [0086] and replace it with the following paragraph:

[0086] Blood sampling (one drop) was performed via the tail tip and glucose levels were determined using a hand-held glucometer (Model: **ONE TOUCH ULTRA™**, Lifescan Canada). Blood glucose levels were determined from all animals once prior to administration (pre-dose), and at 1, 2, 3, 4, 6, 24, 30, 48 and 72 hours post-dose.

Please delete paragraphs [0092] and [0093] and replace them with the following paragraphs:

[0092] Rh insulin, the insulin derivative of example III and the conjugate of the insulin derivative of Example III were administered to 7-8 week-old male **CD®** rats either at 36 nmol/kg sc or 12 nmol/kg intravenously (iv). Blood samples were collected up to 72 hours (only up to 3 hours for rh insulin-treated animals). The drug levels were determined using a human insulin ELISA kit (Linco). The pharmacokinetic parameters were calculated by non-compartmental analysis using the WinNonlin software, N=4 rats per compound/route. FIG. 15 is the pharmacokinetic profile of insulin in normal SD rats where insulin was administered sc at 36 nmol/kg and iv at 12 nmol/kg. FIG. 16 is the pharmacokinetic profile of the conjugate of example III in normal SD rats where the conjugate was administered sc at 36 nmol/kg and iv at 12 nmol/kg. FIG. 17 is the pharmacokinetic profile of the insulin derivative of example III in normal SD rats where the insulin derivative was administered sc at 36 nmol/kg and iv at 12 nmol/kg. FIG. 18 is the subcutaneous PK profile of the administration of insulin, insulin derivative of example III and the conjugate of the insulin derivative of example III. FIG. 19 is the intravenous PK profile of the administration of insulin, insulin derivative of example III and the conjugate of the insulin derivative of example III.

[0093] Diabetes was induced in male **CD®** rats with a single i.v. injection of streptozotocin (60 mg/kg). Two days later, rats received a single sc injection of DAC®:Insulin derivatives at 120 nmol/kg, preformed conjugates at 300 nmol/kg, rh insulin at 20 U/kg (120 nmol/kg) or vehicle. Blood glucose level were measured with a hand-held glucometer just prior injection and a 1, 2, 3, 4, 6, 8, 10, 11, 24, 30 and 48 hours postdose with 5 rats/groups except for vehicle were 3 rats/group were tested. Glycemia of normal rats ranged from 5.2 to 7.6 mmol/L.

Please delete the Example XV header and replace it with the following header:

Evaluation of the Potency of a **DAC™**:Insulin Derivative and its Corresponding Preformed Conjugate following Repeated Subcutaneous Administration